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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 5/8/00

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-17 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-17 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

1. Applicant's amendment, filed 5/8/00 (Paper No. 11), is acknowledged.
Claims 1 and 13 have been amended.

Claims 1-17 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 5/8/00 (Paper No. 11).
The rejections of record can be found in the previous Office Action (Paper No. 9).

3. Formal drawings and photographs have been submitted which fail to comply with 37 CAR 1.84.
Please see the enclosed form PTO-948.

Applicant is reminded to indicate Figures 3A, 3B and 3C in the Brief Description of the Drawings.

4. Claims 1-8, 11, and 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating viral encephalitis with "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification, does not reasonably provide enablement for any "agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 5/8/00 (Paper No. 11), have been fully considered but are not convincing essentially for the reasons of record set forth in Paper No. 9.

Applicant argues that pages 9-10 and 15 provides for agents that specifically inhibit VCAM-1 binding to the α4 subunit of VLA-4.

Upon reconsideration of applicant's arguments and the disclosure of particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification; such peptides are considered enabled.
It is noted that these peptides disclosed in WO 96/01644.
However, should recite these peptides in the claims.

However, applicant appears to rely upon the disclosure of other peptides disclosed in WO 96.22966; WO 96/20216; WO 96/00581 and WO 9606108 as well as U.S. Patent No. 5,510,332 (1449; #AB).
Here, it appears applicant is attempting to incorporate by reference essential subject matter to non-U.S. Patents.
In contrast to relying upon either SEQ ID NOS: 3/4/5 or U.S. Patent No. 5,510,332 which are disclosed in the instant specification as filed; applicant is attempting to incorporate by reference essential subject matter either to non-U.S. Patents or to material not disclosed in the application as filed.

The following is noted.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

As pointed out previously for example; it has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Applicant has not enabled structurally related nor unrelated compounds comprising "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "any agent that specifically bind the alpha-4 subunit of VLA-4". Such structurally unrelated compounds/agents would be expected to have greater differences in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any agent that "inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin" or "that specifically bind the alpha-4 subunit of VLA-4", for the number of possibilities associated with the myriad of direct and indirect effects associated with various adhesion pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin"or "that specifically bind the alpha-4 subunit of VLA-4", and still provide or maintain sufficient activity to treat viral encephalitis would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Again, applicant is invited to recite the particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification into the claimed methods.

Otherwise, applicant's arguments have been fully considered but are not found convincing essentially for the reasons of record, as the claims read on any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

Applicant's arguments have not been found persuasive with the breadth of "agents that inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

5. Upon reconsideration of applicant's amended claim 13, filed 5/8/00 (Paper No. 11); the previous requirement for the biological deposit of the 21.6 antibody/hybridoma under the enablement requirements of 35 USC 112, first paragraph, has been obviated.

6. Upon reconsideration of applicant's amended claim 13, filed 5/8/00 (Paper No. 11); the previous rejection under 35 U.S.C. § 112, second paragraph, has been withdrawn.

7. Upon reconsideration of applicant's amended claims ('wherein said patient is free of multiple sclerosis) and arguments, filed 5/8/00 (Paper No. 11); the previous rejection under 35 U.S.C. § 102(e) as being anticipated by Bendig et al. (U.S. Patent No. 5,840,299), as evidenced by Sanders et al. (Archives of Neurology 53: 125-133, 1996) AND/OR Editorial (Archives of Neurology, 53: 123-124, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105, 1997; 1449), has been withdrawn.

8. Upon reconsideration of applicant's amended claims ('wherein said patient is free of multiple sclerosis) and arguments, filed 5/8/00 (Paper No. 11); the previous rejection under 35 U.S.C. § 102(b) as being anticipated by Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) has been withdrawn..

9. Upon reconsideration of applicant's amended claims ('wherein said patient is free of multiple sclerosis) and arguments, filed 5/8/00 (Paper No. 11); the previous rejection under 35 U.S.C. § 102(a)(b) as being anticipated by Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449) has been withdrawn.

10. Claims 1-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449).

Claims 1-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Soilu-Hanninen et al. (Scand. J. Immunol. 43: 727, 1996) AND/OR Soilu-Hanninen et al. (J. Neuroimmunol. 72: 95-105; 1997; 1449), as applied to claims above and in further view of the art known role or etiology of various viruses inducing encephalitis, as evidenced by Planz et al. (J. Virol. 69: 896-903, 1995; 1449)
AND/OR
the role herpes viruses in multiple sclerosis, as taught by Sanders et al. (Archives of Neurology 53: 125-133, 1996) AND/OR Editorial (Archives of Neurology, 53: 123-124, 1996)

Applicant's arguments, filed 5/8/00 (Paper No. 11), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 9.

Applicant argues the presently claimed methods are direct ed to treating viral encephalitis by blocking adhesion of t cells with brain endothelial cells. Applicant relies upon the complexity of studies of Borna disease (e.g. pages 4-5 of the instant specification) to indicate the lack of predictability of blocking binding of α4-integrin on T cells to VCAM-1 on brain endothelial cells. . Applicant further argues that Bendig and Soilu-Hanninen et al. do not provide sufficient motivation in treating viral encephalitis.

While it is noted that the claimed methods are distinguished from multiple sclerosis; it appears the combined teachings are consistent with the role of T cells in viral inflammation encompassing viral encephalitis and that there was sufficient motivation and expectation of success in inhibiting T cells via blocking VLA-4:VCAM-1 interactions to treat said viral inflammatory conditions wherein T cells contribute to the inflammation at the time the invention was made.

As pointed out previously, Bendig et al. teach using VLA-4α-specific antibodies, including the 21.6 specificity to treat encephalitis (see entire document, including VII. Methods of Treatment on columns 14-16) treating encephalitis and multiple sclerosis).

Also, as pointed out previously; Soilu-Hanninen et al. teach using VLA-4α-specific antibodies to treat virus-facilitated EAE, including its implications relapses triggered by viral infections in multiple sclerosis and by arboviruses (see entire documents). Soilu-Hanninen et al teach that viral infections serve as triggers of relapse phases of multiple sclerosis and the relationship of viral infection with the facilitation of leukocyte entry into the CNS (see entire document, including the Abstract, Introduction and Discussion, 1997).

In contrast to applicant's arguments on lack of predictability; Planz et al. teach the role of T cell subsets in borna disease virus induce progressive encephalitis (see entire document).

Also, both Archives of Neurology citations disclosed that herpes is a common neurotropic virus which was present in more multiple sclerosis patients than control cases (see entire documents).

Therefore, given the clear teaching of treating encephalitis and/or multiple sclerosis with VLA-4α-specific antibodies, as well as the combined teaching that viral infections can serve as triggers of relapse phases of multiple sclerosis as taught by Soilu-Hanninen et al. Or that viral infections can lead to encephalitis as taught by Planz et al. or that herpes viruses are associated with multiple sclerosis; treating patients populations encompassing symptomatic, asymptomatic and pediatric patients would have been targeted by the ordinary artisan at the time the invention was made. Also, given the viral component of encephalitis sclerosis; the ordinary artisan would have provide standard antiinflammatory and antiviral treatment in addition to VLA-4α-specific antibodies at the time the invention was made to inhibit the T cell component of the inflammatory disease.

Applicant's arguments are not found persuasive.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
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July 31, 2000